Title	Scratching and IVF: any role?
Author(s)	Ko, KYJ; Ng, EHY
Citation	Current Opinion in Obstetrics & Gynecology, 2016, v. 28 n. 3, p. 178-183
Issued Date	2016
URL	http://hdl.handle.net/10722/234868
Rights	This is a non-final version of an article published in final form in Current Opinion in Obstetrics & Gynecology, 2016, v. 28 n. 3, p. 178-183; This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

Scratching and IVF: any role?

Jennifer Ka Yee Ko, Ernest Hung Yu Ng

Department of Obstetrics and Gynaecology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Corresponding author
Jennifer K.Y. Ko
Email address: jenko@hku.hk

Telephone number: +852 22554647
Fax number: +852 28550947

Abstract
Purpose of review: To review updated information on the influence of endometrial scratching on in vitro fertilization (IVF).

Recent findings: Endometrial receptivity remains an important rate-limiting step affecting the success of IVF. The current evidence on the effect of endometrial scratching on IVF ranges from marked improvement, no difference to a potentially negative impact. The heterogeneity of studies presents a challenge in interpretation of data for routine clinical practice.

Summary: Endometrial scratching performed in the preceding cycle is associated with improved clinical pregnancy and live birth rates in women with recurrent implantation failure (RIF), but not in unselected subfertile women undergoing IVF. Most of the current literature are underpowered and at high risk of bias.

Keywords: clinical pregnancy, endometrial biopsy, implantation failure, in-vitro fertilization

Introduction

Infertility is an important public health issue affecting up to 1 in 6 couples[1]. With ever-increasing demands in assisted reproductive techniques, there is constant pressure to improve in vitro fertilization (IVF) success rates. Amidst the huge amounts invested into improving assisted reproductive techniques, endometrial receptivity remains an important rate-limiting step affecting the success of IVF.

Endometrial scratching refers to intentional local mechanical injury of the endometrial lining with the aim to improve endometrial receptivity. It is commonly performed using a pipelle biopsy or curettage in an outpatient setting, although the use hysteroscopy has also been described. The first observation that endometrial scratching possibly increased pregnancy rates came from animal studies, when Loeb reported in 1907 that endometrial injury induced rapid proliferation of decidual cells in the guinea pig uterus[2]. Similarly, decidualization was demonstrated when oil was infused into rats' uterus to cause local injury[3].

In 2003, Barash et al reported in a prospective randomized controlled trial that repeated local injury to the endometrium in the cycle preceding IVF doubled the incidence of successful pregnancies in 134 patients with history of one or more failed cycles undergoing IVF [4]. In the extreme case, endometrial scratching has been suggested to increase endometrial thickness in Asherman syndrome, and even resulted in successful implantation of embryo and live birth[5-7].

The issue of whether to scratch or not to scratch has been widely debated. The current evidence on the effect of endometrial scratching on IVF ranges from marked improvement, no difference to a potentially negative impact. Proponents of endometrial scratching would argue that compared with the high costs of IVF, it is a simple and low cost intervention that could possibly improve implantation rates, so why not? On the other hand, there is great danger in widely adopting intervention that has no proven benefit, or may even cause potential harm.

In this review, we aim to summarize evidence on the role of endometrial scratching in IVF.

Recurrent implantation failure (RIF)

There are different definitions for RIF[8]. In general, RIF is defined as failure to achieve pregnancy after 2-6 IVF cycles over which more than 10 good quality embryos were transferred[9]. Other authors propose RIF as the failure to achieve a clinical pregnancy after transfer of at least 4 good-quality embryos in a minimum of 3 fresh or frozen cycles in a woman under the age of 40 years[10]. RIF may be caused by problems with endometrial receptivity, embryonic development or in many cases, multifactorial. Unexplained implantation failure is when embryos fail to implant in the presence of good ovarian response, high quality embryos, satisfactory endometrial development and no identifiable cause. Women with RIF represent a high-risk group of further failed IVF cycles

and are precisely those who could potentially benefit the most from endometrial scratching, should the intervention be useful in improving IVF outcomes.

A systemic review and meta-analysis investigated the effect of endometrial scratching specifically in women with RIF[11]. The review included 2062 participants from 4 randomized and 3 non-randomized controlled trials. Women in the studies had history of 1-6 previous failed IVF attempts. All were subjected to endometrial injury in the cycle preceding ovarian stimulation although endometrial injury induced by both endometrial scratch and hysteroscopy were included. Hysteroscopy was performed at the early proliferative phase in the hysteroscopy studies and the number of endometrial scratches ranged from 1-4 times in the endometrial scratching studies. Pooling of the studies concluded that local endometrial injury in the cycle preceding ovarian stimulation was 70% more likely to result in a clinical pregnancy compared to no intervention.

Data from recent retrospective studies did not show an improved pregnancy outcome in the endometrial scratch group[12, 13]. Werner et al studied the impact of a single endometrial scratch in those who have failed to conceive despite transfer of morphologically normal euploid blastocysts to minimize the effect of an embryonic cause of implantation failure in the study participants[12]. Similarly, embryo quality is expected to be good in the study by Dain et al, which evaluated the influence of endometrial injury in 737 donor oocyte cycles[13]. Nevertheless, the retrospective nature of both studies limited the conclusions that can be drawn from them.

Majority of the randomized controlled trials did show better pregnancy outcomes in women with RIF who had endometrial injury in the preceding cycle. The two randomized controlled trials included in the meta-analysis by Potdar et al showed higher implantation and clinical pregnancy rates in the intervention compared to the non-intervention group[11, 14, 15]. Narvekar et al randomized 100 good responders with RIF into the endometrial scratching group, which was done once at the follicular phase and again in the luteal phase of the preceding cycle. It is worth noting that the control group also underwent hysteroscopy on day 7-10 of the preceding cycle, which could have caused mild endometrial injury[14]. Endometrial scratching was performed once on days 21-26 of the preceding cycle in the study by Karimzadeh et al involving 115 women with RIF[15]. Shohayeb et al also found a higher implantation rate (12% vs 7%, $p=0.015$), clinical pregnancy rate (32% vs 18%, $p=0.034$) and live birth rate (28% vs 14%, $p=0.024$) in 210 women with RIF who underwent endometrial scratching compared to controls[16]. Endometrial injury was performed using a Novak curette during hysteroscopy on day 4-5 of the preceding cycle. Similar to the study by Narvekar et al[14], the non-intervention group also had hysteroscopy, which could have influenced the endometrium. Women with abnormal uterine cavity by transvaginal ultrasound or by hysterosalpingography were excluded.

Two other randomized controlled trials did not show a beneficial effect in women subjected to endometrial scratching in the preceding cycle[17, 18].

Baum et al performed a double blinded randomized controlled study involving 36 patients with RIF, defined as 3 or more unsuccessful cycles of IVF-ET with good ovarian response, who were randomized to endometrial scratching twice (on days 9-12 and 21-24 of menstrual cycle) preceding IVF treatment and no intervention. The study showed a lower implantation rate (2.08% versus 11.1%, p=0.1), clinical pregnancy rate (0% vs 31.25%, p< 0.05) and live birth rate (0% versus 25%, p = 0.1) in the intervention group[17]. One of the strengths of that study was that women in the control group had to undergo a 'placebo' intervention at which the biopsy catheter was introduced in the cervix without endometrial injury, but the study was underpowered. In another more recent randomized controlled trial, although there was no statistical difference in live birth rate between those who had endometrial scratching versus control, further analysis showed that endometrial scratching improved live birth rate in women with 2 or more previous IVF failures but not in those with history of 1 failed IVF cycle[18].

Non-RIF

Several studies evaluating the effect of endometrial scratching on IVF were performed on women without RIF.

Zhou et al recruited good responders who had irregular endometrial echoes diagnosed on ultrasound during the stimulation cycle and performed endometrial scratching until the strong echoes disappeared on ultrasound. They demonstrated higher implantation (33.33% vs 17.78%), clinical pregnancy (48.33% vs 27.86%), and ongoing or live birth rates per embryo transfer (41.67% vs 22.96%) in the endometrial scratching group compared to controls[19]. There were no information or details about these irregular endometrial ultrasound echoes.

Nastri et al performed pipelle endometrial scratch once in an oral contraceptive pill pre-treatment cycle 7-14 days preceding ovarian stimulation in an unselected population of women undergoing IVF and found increased live birth and clinical pregnancy rates without effect on miscarriage and multiple pregnancy rates compared to controls[20]. However, it should be noted that 44/79 (55.7%) of the women in that study did have at least two previous unsuccessful embryo transfers. Moreover, the study was terminated early because the interim analysis showed a significant benefit in the endometrial scratching group and therefore underpowered.

Similarly, the study by Guven et al found a higher clinical pregnancy (48.2% vs 29.0%, p=0.025) and live birth (33.9% vs 17.7%, p=0.035) rates in the intervention group compared to controls, although in Guven's study, endometrial scratching was performed on day 3 of the transfer cycle rather than the preceding cycle[21].

In contrast, Karimzade et al found a negative impact on implantation (7.9% vs 22.9%, p=0.002), clinical pregnancy (12.3% vs 32.9%, p=0.004) and ongoing pregnancy (9.6% vs 29.1%, p=0.004) outcomes in a prospective controlled trial

involving 156 patients who had local injury to the endometrium on the day of oocyte retrieval using a Novak curette[22].

Safdarian et al randomized 100 good responders to the endometrial scratching group on day 21 of the preceding cycle or control, and did not find a significant difference in the implantation and clinical pregnancy rates between the groups. Cancellation rate was unacceptably high in that study[23].

Yeung et al conducted an adequately powered randomized controlled study recruiting 300 unselected subfertile women undergoing IVF. Women with uterine cavity abnormalities on saline infusion sonogram or hysteroscopy were excluded. Endometrial injury was induced by an endometrial scratch using a pipelle catheter at the mid-luteal phase of the preceding cycle. Our study did not find a significant difference in the on-going pregnancy, implantation, clinical pregnancy, miscarriage and multiple pregnancy rates between the endometrial scratching and non-intervention groups[24]. In the subgroup analysis of women undergoing repeated IVF cycles, the ongoing pregnancy rate was significantly lower in the endometrial scratching group than in the non-intervention group.

Hysteroscopy

Hysteroscopy has been described as a means of inducing local endometrial injury in some studies. Systemic reviews and meta-analyses on the effect of hysteroscopy on IVF showed higher clinical and live birth rates associated with the procedure before IVF, although a significant proportion of the evidence came from non-randomized trials[25, 26]. Part of the improvement could be related to the identification and correction of intrauterine abnormalities including endometrial polyps and submucosal fibroid by hysteroscopy, which could be identified in up to 25-50% women with RIF[27]. However, even when those with normal uterine cavity were analysed separately, there was a significant improvement in the outcome of the normal hysteroscopy group compared with controls (RR = 1.64, 95% CI 1.35-1.98, $P < 0.001$)[26], suggesting that hysteroscopy may also improve pregnancy outcomes by other means, such as subsequently resulting in easier and more precise embryo transfer or inducing endometrial injury[25]. Nevertheless, the trophy trial, a multicenter randomized study involving 8 European IVF centres where outpatient hysteroscopy was performed in patients with 2-4 failed IVF ET cycles prior to starting IVF treatment, did not find a difference in clinical pregnancy rate between hysteroscopy and control groups[28].

Pathophysiology

There is no doubt that successful implantation depends on a myriad of factors involving several cytokines and growth factors in an intricate crosstalk between the embryo and endometrium. The original observation was that local injury to the endometrium induced decidualization, thereby increasing the probability of implantation of the embryo[2, 3]. As decidua sheds with the onset of menstruation, this theory does not fully explain the improved outcome found in

studies that performed endometrial scratching in the cycle preceding the transfer cycle or even prior to that.

Gnainsky et al reported that local injury to the endometrium produced an inflammatory response resulting in a significantly increased amount of macrophage, dendritic cells and proinflammatory cytokines including tumour necrosis-α (TNF-α), growth-regulated oncogene-α (GRO-α), interleukin-15 (IL-15) and macrophage inflammatory protein 1B (MIP-1B)[29]. In particular, increased levels of TNF-α and MIP-1B have been detected during the window of implantation, suggesting the role of inflammation in development of a receptive endometrium[30]. Pro-inflammatory cytokines stimulate endometrial stromal cells to attract monocytes and induce their differentiation into dendritic cells, which then upregulate a wide variety of genes involved in preparing the endometrium for embryo implantation[31, 32].

High oestradiol concentrations during ovarian stimulation have also been found to lead to premature progesterone elevation, causing endometrial advancement and hampering implantation related to asynchrony of the endometrium with the embryo stage[33]. One further theory is that endometrial injury corrects this asynchrony[34].

Side effects

Endometrial injury can be performed using a pipelle catheter as an outpatient procedure in majority of the cases without complications. However, Nastri et al reported increased pain associated with the procedure (mean visual analogue scale 6.42+/- 2.35 vs 1.82 +/- 1.52, $p<0.001$)[20].

Recent Development

Many of the current systemic reviews and meta-analyses are based on non-randomized trials. Several studies were lacking in adequate power. Moreover, a major limitation is the heterogeneity in studies with regard to the recruited study subjects, timing of endometrial scratch, method and number of endometrial scratches performed, which limits the conclusions that can be drawn from them. This heterogeneity is illustrated by the systemic review by El-Toukhy et al, among many others[35]. Consisting of 2 randomized and 6 non-randomized studies, the number of previous IVF attempt in the included studies varied from 1 to 4. Endometrial scratching was performed in the cycle preceding stimulation in 5 studies and in the transfer cycle in 3 other studies. The frequency of endometrial scratching also varied: once in 5 studies, twice in 2 studies and 4 times in one study.

While a previous Cochrane review in 2012 only 5 randomized controlled trials[36], the latest version in 2015 included 14 trials involving 1063 in the intervention group and 1065 women in the control group[37]. With increasing evidence available, it is timely to revisit the effectiveness of endometrial injury in different subgroups of women undergoing IVF to aid decisions in clinical practice. Endometrial scratching performed between day 7 of the previous cycle

and day 7 of the embryo transfer cycle does appear to improve the pregnancy outcomes in women with more than 2 previous embryo transfers(37). Questions remain whether to extend this intervention to a wider group. Evidence currently shows that it is not acceptable to perform endometrial scratching routinely on all women undergoing IVF. This evidence is considered to be moderate quality. Well-designed and adequate powered trials that avoid instrumentation of the uterus in the preceding three months, do not cause endometrial damage in the control group, stratify the results for women with and without RIF and report live birth are needed.

Conclusions

Endometrial scratching performed in the preceding cycle is associated with improved clinical pregnancy and live birth rates in women with RIF, but not in unselected subfertile women undergoing IVF.

Key points

- Endometrial scratching performed in the preceding cycle is associated with improved clinical pregnancy and live birth rates of IVF treatment in women with RIF but the quality of evidence is moderate only.
- There is no improvement in clinical pregnancy and live birth rates of IVF treatment in unselected subfertile women.
- A negative IVF outcome is found when endometrial scratching is performed on the day of the retrieval.

Acknowledgements

None

Financial support and sponsorship

None

Conflict of interest

The authors report no conflicts of interest.

References

•special interest

•• outstanding interest

1. ESHRE ART Fact Sheet July 2014. https://http://www.eshre.eu/guidelines-and-legal/art-fact-sheet.aspx (Accessed 22/12/2015).
2. Loeb L. The experimental proof changes in the uterine decidua of guinea pig after mating. Zentralbl Allg Pathol. 1907;18:563-5.
3. Humphrey KW. Interactions between oestradiol 3, 17 beta and progesterone on the induction and growth of deciduomata in ovariectomized mice. Australian journal of biological sciences. 1969;22(3):689-99.
4. Barash A, Dekel N, Fieldust S, et al. Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization. Fertility and sterility. 2003;79(6):1317-22.
5. Barash A, Granot I, Fieldust S, Or Y. Successful pregnancy and delivery of a healthy baby after endometrial biopsy treatment in an in vitro fertilization patient with severe Asherman syndrome. Fertility and sterility. 2009;91(5):1956 e1-3.
6. Gargett CE, Healy DL. Generating receptive endometrium in Asherman's syndrome. Journal of human reproductive sciences. 2011;4(1):49-52.
7. Nagori CB, Panchal SY, Patel H. Endometrial regeneration using autologous adult stem cells followed by conception by in vitro fertilization in a patient of severe Asherman's syndrome. Journal of human reproductive sciences. 2011;4(1):43-8.
8. Polanski LT, Baumgarten MN, Quenby S, et al. What exactly do we mean by 'recurrent implantation failure'? A systematic review and opinion. Reproductive biomedicine online. 2014;28(4):409-23.
9. Tan BK, Vandekerckhove P, Kennedy R, Keay SD. Investigation and current management of recurrent IVF treatment failure in the UK. BJOG : an international journal of obstetrics and gynaecology. 2005;112(6):773-80.
10. Coughlan C, Ledger W, Wang Q, et al. Recurrent implantation failure: definition and management. Reproductive biomedicine online. 2014;28(1):14-38.
11. Potdar N, Gelbaya T, Nardo LG. Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis. Reproductive biomedicine online. 2012;25(6):561-71.
12. Werner MD, Forman EJ, Hong KH, et al. Endometrial disruption does not improve implantation in patients who have failed the transfer of euploid blastocysts. Journal of assisted reproduction and genetics. 2015;32(4):557-62.
13. Dain L, Ojha K, Bider D, et al. Effect of local endometrial injury on pregnancy outcomes in ovum donation cycles. Fertility and sterility. 2014;102(4):1048-54.
14. Narvekar SA, Gupta N, Shetty N, et al. Does local endometrial injury in the nontransfer cycle improve the IVF-ET outcome in the subsequent cycle in patients with previous unsuccessful IVF? A randomized controlled pilot study. Journal of human reproductive sciences. 2010;3(1):15-9.
15. Karimzadeh MA, Ayazi Rozbahani M, Tabibnejad N. Endometrial local injury improves the pregnancy rate among recurrent implantation failure

patients undergoing in vitro fertilisation/intra cytoplasmic sperm injection: a randomised clinical trial. The Australian & New Zealand journal of obstetrics & gynaecology. 2009;49(6):677-80.
16. Shohayeb A, El-Khayat W. Does a single endometrial biopsy regimen (S-EBR) improve ICSI outcome in patients with repeated implantation failure? A randomised controlled trial. European journal of obstetrics, gynecology, and reproductive biology. 2012;164(2):176-9.
17. Baum M, Yerushalmi GM, Maman E, et al. Does local injury to the endometrium before IVF cycle really affect treatment outcome? Results of a randomized placebo controlled trial. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. 2012;28(12):933-6.
18. Gibreel A, El-Adawi N, Elgindy E,et al. Endometrial scratching for women with previous IVF failure undergoing IVF treatment. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. 2015;31(4):313-6.
19. Zhou L, Li R, Wang R, et al. Local injury to the endometrium in controlled ovarian hyperstimulation cycles improves implantation rates. Fertility and sterility. 2008;89(5):1166-76.
20. Nastri CO, Ferriani RA, Raine-Fenning N, Martins WP. Endometrial scratching performed in the non-transfer cycle and outcome of assisted reproduction: a randomized controlled trial. Ultrasound in obstetrics & gynecology. 2013;42(4):375-82.
21. Guven S, Kart C, Unsal MA, et al. Endometrial injury may increase the clinical pregnancy rate in normoresponders undergoing long agonist protocol ICSI cycles with single embryo transfer. European journal of obstetrics, gynecology, and reproductive biology. 2014;173:58-62.
22. Karimzade MA, Oskouian H, Ahmadi S, Oskouian L. Local injury to the endometrium on the day of oocyte retrieval has a negative impact on implantation in assisted reproductive cycles: a randomized controlled trial. Archives of gynecology and obstetrics. 2010;281(3):499-503.
23. Safdarian L, Movahedi S, Aleyasine A, et al. Local injury to the endometrium does not improve the implantation rate in good responder patients undergoing in-vitro fertilization. Iranian journal of reproductive medicine. 2011;9(4):285-8.
•24. Yeung TW, Chai J, Li RH, et al. The effect of endometrial injury on ongoing pregnancy rate in unselected subfertile women undergoing in vitro fertilization: a randomized controlled trial. Hum Reprod. 2014;29(11):2474-81.
An adequately powered randomized controlled trial performed in 300 unselected womenw ith subfertility undergoing IVF
25. Pundir J, Pundir V, Omanwa K, et al. Hysteroscopy prior to the first IVF cycle: a systematic review and meta-analysis. Reproductive biomedicine online. 2014;28(2):151-61.
26. El-Toukhy T, Sunkara SK, Coomarasamy A, et al. Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. Reproductive biomedicine online. 2008;16(5):712-9.
27. Makrakis E, Pantos K. The outcomes of hysteroscopy in women with implantation failures after in-vitro fertilization: findings and effect on

subsequent pregnancy rates. Current opinion in obstetrics & gynecology. 2010;22(4):339-43.
28. El-Toukhy T, Khalaf Y, Coomarasamy A, et al. . A multicentre randomized study of pre-IVF outpatient hysteroscopy in women with recurrent IVF-ET failure—The trophy trial. (Abstract). Presented at the ESHRE annual meeting. 2014.
29. Gnainsky Y, Granot I, Aldo PB, et al. Local injury of the endometrium induces an inflammatory response that promotes successful implantation. Fertility and sterility. 2010;94(6):2030-6.
30. Haider S, Knofler M. Human tumour necrosis factor: physiological and pathological roles in placenta and endometrium. Placenta. 2009;30(2):111-23.
31. Kalma Y, Granot I, Gnainsky Y, et al. Endometrial biopsy-induced gene modulation: first evidence for the expression of bladder-transmembranal uroplakin Ib in human endometrium. Fertility and sterility. 2009;91(4):1042-9, 9 e1-9.
32. Gnainsky Y, Granot I, Aldo P, et al. Biopsy-induced inflammatory conditions improve endometrial receptivity: the mechanism of action. Reproduction. 2015;149(1):75-85.
33. Fatemi HM, Popovic-Todorovic B. Implantation in assisted reproduction: a look at endometrial receptivity. Reproductive biomedicine online. 2013;27(5):530-8.
34. Li R, Hao G. Local injury to the endometrium: its effect on implantation. Current opinion in obstetrics & gynecology. 2009;21(3):236-9.
35. El-Toukhy T, Sunkara S, Khalaf Y. Local endometrial injury and IVF outcome: a systematic review and meta-analysis. Reproductive biomedicine online. 2012;25(4):345-54.
36. Nastri CO, Gibreel A, Raine-Fenning N, et al. Endometrial injury in women undergoing assisted reproductive techniques. Cochrane Database Syst Rev. 2012;7:CD009517.
37. Nastri CO, Lensen SF, Gibreel A, et al. Endometrial injury in women undergoing assisted reproductive techniques. Cochrane Database Syst Rev. 2015;3:CD009517.
••The latest Cochrane review evaluating the effect of endometrial injury on IVF

Word count 2360

RIF studies						
Author	**Trial design**	**Sample size**	**Endometrial scratch timing**	**Number of endometrial scratch**	**Journal with Impact factor**	**Outcome**
Karimzadeh 2009	RCT	115	Preceding cycle Day 21-26	1	Yes	Increase in IR and CPR
Narvekar 2010	RCT	100	Preceding cycle Day 7-10 and 24-25	2	No	Increase in IR, CPR and LBR
Shohayeb 2012	RCT	210	Preceding cycle Day 4-7 during hysteroscopy	1	Yes	Increase in IR, CPR and LBR
Baum 2012	RCT	36	Preceding cycle Day 9-12 and 21-24	2	Yes	No difference in IR and LBR, decrease in CPR
Gibreel 2015	RCT	387	Preceding cycle Day 21-26 and after initiation of GnRHa in long agonist protocols	2	Yes	No difference in CPR and LBR
Dain 2014	Retrospective	737 Donor oocyte cycles	Preceding cycle, day 20-22 or 1-2 weeks preceding ovum donation cycle	1	Yes	No difference in CPR and LBR
Werner 2015	Retrospective	290	Preceding 1-2 cycles, luteal phase	1	Yes	No difference in clinical IR and sustained IR
Non-RIF studies						

Zhou 2008	Yes	121	Transfer cycle Day 5-22	?1	Yes	Increase in IR, CPR and LBR
Karimzade 2010	Yes	156	Transfer cycle, day of oocyte retrieval day	1	Yes	Decrease in IR, CPR and OPR
Safdarian 2011	RCT	100	Preceding cycle, day 21	1	Yes	No difference in IR and CPR
Nastri 2013	RCT	158	Preceding cycle 7- 14 days before COS	1	Yes	Increase in CPR and LBR
Guven 2014	RCT	118	Transfer cycle Day 3	1	Yes	Increase CPR and LBR
Yeung 2014	RCT	300	Preceding cycle LH+7 or day 21	1	Yes	No difference in IR, CPR and LBR

Table 1. Summary of the studies. RIF- recurrent implantation failure, RCT- randomized controlled trial, IR- implantation rate, CPR- clinical pregnancy rate, LBR- live birth rate, OPR- ongoing pregnancy rate, COS- controlled ovarian stimulation, LH+7 – 7 days after LH surge